REMARKS

New claim 51 has been added. This claim is identical to claim 36, except with the additional limitation that the compound identified using the assay is a partial agonist. Support for this amendment may be found, for example, in the specification as filed at page 14, line 19. No further amendments have been made herein. The pending claims are 36-47 and 51.

Claims 36-47 stand rejected as being obvious under 35 U.S.C. § 103(a) in view of U.S. Patent No. 6,444,666 (Ladduwahetty et al.). Applicants respectfully disagree with the Examiner's analysis and submit that the reference does not suggest the claimed invention.

Ladduwahetty is concerned with providing compounds for the treatment of various disorders of the central nervous system and mentions anxiety disorders and depressive disorders. Applicants previously noted that Ladduwahetty mentions properties that are desired for anxiolytics, but stressed that there is nothing in the cited references, or the prior art as a whole, that suggests that an assay for anxiolytic compounds would also identify antidepressants. The necessary connection between the pharmacologic actions of anxiolytics and antidepressants just does not exist in the prior art.

The Examiner states in the Office Action at the bottom of page 3 and the middle of page 4 that Ladduwahetty teaches selectivity "and then immediately provides examples, including depression, at lines 37-38." Applicants respectfully disagree with this reading of the reference and submit that it is incorrect. In fact, Ladduwahetty describes binding selectivity in the context of anxiety, then discusses the use of antagonists or inverse agonists to reverse sedation or hypnosis, and only then goes on to a new paragraph listing a collection of diseases treatable with "[t]he compounds of the present invention." Ladduwahetty's description is limited to:

(1) a medical use for functional agonists at $\alpha 1\beta\gamma 2$, $\alpha 2\beta\gamma 2$ and $\alpha 3\beta\gamma 2$ subunits (anxiolysis, see column 2, lines 10-12);

(2) a separate description of binding parameters that characterize certain preferred compounds for use as anxiolytics ("it is considered that $GABA_A$ receptor agonists which bind more effectively to the $\alpha 2$ and/or $\alpha 3$ subunit than to α_1 will be effective in the treatment of anxiety with a reduced propensity to cause sedation", column 2, lines 20-24);

(3) medical uses for $\alpha 1$ antagonists and inverse agonists (anti-sedation and anti-hypnosis, see column 2, lines 24-26); and

(4) a list of anxiety- and depression- related illnesses amenable to treatment with "compounds of the present invention" (column 2, lines 27-40).

There are at least two substantial gaps in this disclosure. First, Ladduwahetty does not teach or suggest the use of EC50 values at particular receptor subtypes to select compounds for the treatment of any particular disorder. Applicant's claims require determining compound EC_{50} values at an $\alpha_2\beta_3\gamma_2$ $GABA_A$ subtype receptor or an $\alpha_3\beta_3\gamma_2$ $GABA_A$ subtype receptor. As described in Applicants' specification, EC_{50} values do not necessarily correlate with binding affinities or efficacies (page 8, lines 1-15), and the claimed methods may be performed without measuring binding affinities (page 7, lines 12-14). Binding affinity was the basis for conventional screening methods for receptor-selective compounds. See Paul J. Whiting, "The $GABA_A$ receptor gene family: New opportunities for drug development," 6 Current Opinion in Drug Discovery & Development, 648-57, 652 (2003) (copy provided with this paper) ("The traditional approach to develop compounds that are selective for, for example, a receptor subtype, is to aim for binding affinity or selectivity, which can be achieved through the use of conventional radioligand binding assays.") In keeping with the traditional approach, Ladduwahetty describes selectivity only in the context of binding. The skilled artisan reading

Ladduwahetty would be taught that binding affinity is the important parameter, and conduct conventional screening assays based on binding affinity, not on efficacy and EC_{50} values. Thus Ladduwahetty does not teach or suggest the claimed assay.

Second, Ladduwahetty provides no teaching as to which of the listed conditions could be treated with compounds exhibiting any particular combination of agonism, antagonism, or inverse agonism at any of the α_1, α_2, α_3, β, and γ subunits for which some binding parameters are specified. The reference to depression at column 2, line 37, occurs in a paragraph describing uses for "the compounds of the present invention." This phrase is defined by Ladduwahetty at column 3, lines 3-18, to encompass compounds with the binding selectivity described in the column 2, lines 10-26 passage, as well as compounds that do not display such binding selectivity. See, in particular, column 3, lines 12-15: "compounds which are unselective in terms of their binding affinity for the α2 and/or α3 subunit relative to the α1 subunit are also encompassed within the scope of the present invention…." Nowhere does the reference provide the reader with sufficient information to conclude that binding to, much less selective activation of, certain subunits will result in antidepressant activity in addition or in preference to anxiolytic activity. Ladduwahetty instead seems to suggest that something other than selective interactions with these subunits

accounts for antidepressant activity. Ladduwahetty at column 3, lines 12-18. Thus, Ladduwahetty fails to disclose or suggest the principle that selective activation of α2 or α3 receptor subunits will result in antidepressant effects with minimal sedation or cognitive impairment.

Applicants respectfully suggest that the Examiner is inappropriately using hindsight, and the disclosure of the present application, to fill in the gaps in Ladduwahetty's disclosure. Without applying hindsight, the claimed assay cannot be considered obvious in view of Ladduwahetty. Reconsideration and withdrawal of the § 103(a) rejection based on Ladduwahetty is respectfully requested.

The Applicants urge the Examiner to contact the Applicants' undersigned representative at (312) 913-2114 he believes that a discussion would expedite prosecution of this application.

Respectfully submitted,

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